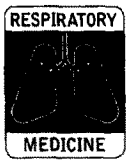
RESPIRATORY MEDICINE (1999) 93, 752–753



Short Communication

Promoter variation of tumour necrosis factor-alpha gene: possible high risk for chronic bronchitis but not diffuse panbronchiolitis

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Introduction

Diffuse panbronchiolitis is a distinctive chronic obstructive pulmonary disease of unknown aetiology and characterized by chronic inflammation around respiratory bronchioles (1). Although many cases have been reported in East Asians, it is extremely rare in Caucasians (2). Familial cases have also been noted in Japanese subjects. These observations raise the possibility that a genetic factor in Asians is implicated in the inflammatory process underlying the pathogenesis of the disease. Recent studies have demonstrated that diffuse panbronchiolitis is strongly associated with the human leukocyte antigen (HLA) genes (3–5). However, the functional consequences of these associations remain unknown and another closely linked gene in the HLA region might determine disease susceptibility (6).

The tumour necrosis factor alpha (TNF-α) gene, encoding a pro-inflammatory cytokine, is located in the HLA class III region and is believed to play a major role in the pathogenesis of many inflammatory and immune-mediated diseases. Of the reported polymorphisms within the TNF-α gene, a guanine-to-adenine substitution at position −308 within its promoter region is of particular interest, because the −308A allele, also known as the TNF-2 allele, has been directly shown to upregulate the transcriptional activity of the TNF gene (7). In fact, the allele is associated with cerebral malaria (8) and mucocutaneous leishmaniasis (9), presumably causing excessive TNF production in the host. More recently, the same allele has been shown to confer a higher risk to the development of chronic bronchitis in an Asian population (10). These findings prompted us to investigate the TNF-α promoter variation in diffuse panbronchiolitis.

Received 29 May 1999 and accepted 7 June 1999.
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0954-6111/99/100752+02 $12·00/0

Methods

We collected DNA samples from 76 patients with diffuse panbronchiolitis, fulfilling the diagnostic criteria as reported previously (4). DNA samples from 87 healthy volunteers from the same area of Japan were analysed simultaneously. The −308 G/A TNFα promoter variation was detected by the method of restriction fragment length polymorphism as described previously (11). Briefly, the corresponding region was amplified by polymerase chain reaction and digested by the *NcoI* restriction enzyme. The digested fragments were then separated on an agarose gel and visualized by ethidium bromide staining.

Results

Only one of the 76 Japanese patients and none of the 87 controls carried the −308A allele (Table 1). The nucleotide substitution was further confirmed by the direct sequencing method (data not shown). The patient, who was heterozygous for −308G/−308A alleles in this study, did not show any distinct clinical findings, as compared with the other patients (data not shown).

Discussion

Diffuse panbronchiolitis is associated with the HLA-B gene (3,4), and the TNF-α gene is located at only 250 kb centromeric of the HLA-B gene. However, the TNF-α variation analysed was not associated with the disease. This finding contrasts with a recent report showing a positive association between the −308A variant and chronic

TABLE 1. Frequencies of the TNFα alleles in patient and control samples

Group	−308G/−308G *n* (%)	−308G/−308A *n* (%)	−308A/−308A *n* (%)	Total *n*
Patient	75 (98·7)	1 (1·3)	0 (0·0)	76
Control	87 (100·0)	0 (0·0)	0 (0·0)	87

bronchitis in Taiwanese (10). Although diffuse panbronchiolitis and chronic bronchitis share characteristics similar to chronic obstructive pulmonary disease, the contribution of TNF-α variation to genetic predisposition appears clearly different between the two diseases. The present study also revealed that the −308A allele is rare in the normal Japanese population. In Caucasians, the frequency of the same allele is much higher (16–27%) (10,11). This would be explained by an ethnic difference in the allele frequency. To elucidate the genetic predisposition for diffuse panbronchiolitis, regional variations in other functional genes in the HLA region should be further investigated.

Acknowledgements

This study was supported by research grants for Surveys and Research on Specific Diseases, from the Ministry of Health and Welfare of Japan in 1997 and 1998.

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